UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,025	04/27/2001	Jennifer Ott Reilly	CIBT-P01-098	1533

28120 7590 10/29/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/845,025	REILLY, JENNIFER OTT	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 10-28* is/are pending in the application.

4a) Of the above claim(s) *5,10 and 13-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth in Paper 17, 5/27/03, have been entered in full.

Claims 5, 10, 13-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

Applicant's election with traverse of Group I, claims 1-4, 6-14 in Paper 17 is acknowledged. The traversal is on the grounds that a search of Group I and of group II would be coextensive and would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) or distinct as claimed (see MPEP § 806.05- §806.05(I)): and
(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, although a search of the polypeptides of Group I would overlap a search of the polynucleotides of Group II, the two searches would not

be coextensive. In many instances, a protein will have been known in the art before the DNA has been discovered that encodes the protein. Often the protein will be known by a name different than the name given the protein after the cloning of the nucleic acid - and may even be associated with a completely different activity than that ascribed to it when the nucleic acid was cloned. Thus, Groups I and II require divergent searches, and to search both inventions would be burdensome. Therefore, the restriction is maintained and made final. Additionally, Applicant is reminded that the claims will be examined only to the extent that the claims are directed to the elected SEQ ID NO: 15, NGF, and cholinergic neurons. The examiner finds that elected claims 1-4, 6, 11 and 12 read on these species.

Drawings

The drawings are objected to as set forth in the attached Notice of Draftsperson's Patent Drawing Review (PTO-948). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: The specification makes reference to specific polynucleotide and/or polypeptide sequences, see page 45 for example; these references must contain a sequence identifier of the form: SEQ ID NO: X. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

Claim 1 recites the phrase "hedgehog therapeutic". The specification defines "hedgehog therapeutic" as that which mimics the effect of naturally occurring hedgehog proteins on hedgehog signaling and includes "agonists" that agonize the effects of naturally occurring hedgehog polypeptide as a neuroprotective agent (see page 10). Thus, "hedgehog therapeutic" appears to encompass any and all compounds that alter the activity of the many different hedgehog proteins as well as the activities of their receptors e.g. patched (ptc-1 and ptc-2). However, it is well appreciated that the activities of these pathways are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40), therefore the phrase "hedgehog therapeutic" renders the claims indefinite because those skilled in the art would have to identify the activities of the known patched and hedgehog polypeptides in order to determine whether a compound alters these activities, as they relate to any neuroprotective effect.

Further the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a

"hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

Claims 11 and 12 are confusing because they require that the neurotrophic factor either "comprises NGF" or "consists essentially of NGF". It is unclear what these phrases are intended to mean, e.g. do they refer to an NGF molecule that may contain additional amino acids or do they refer to a neurotrophic factor that may contain additional growth factors other than NGF? Such a distinction would determine the bound of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting the survival of cholinergic neurons, comprising the administration of a mammalian sonic hedgehog polypeptide (e.g. SEQ ID NO: 15) or the N-terminal autoproteolytic fragment thereof, does not reasonably provide enablement for such methods comprising the administration of polypeptides other than a naturally occurring mammalian sonic hedgehog polypeptide or for the genus of "bioactive fragments" thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents the results obtained with an *in vitro* model of cholinergic cell survival comprising the administration of sonic hedgehog, presumably that of the murine SEQ ID NO: 12, although it does not appear that the specification actually teaches which sonic hedgehog is used. The claims claim methods using any polypeptide that could be termed a "hedgehog" polypeptide, yet the specification has not provided sufficient guidance as to which other polypeptides would work as claimed. One of skill in the art appreciates that the many known hedgehog polypeptides provide for a tremendous and disparate array of developmental controls, determining cell fates in embryonic muscle, lung, and nervous tissues. There is no teaching in the specification as to which of this vast array of proteins, natural or created, could be used in the claimed methods. The prior art is also silent as to which of the proteins, with the exception of sonic hedgehog (see below) could be used to practice the claimed methods. One could only guess at which, if any, could be used; and one of skill in the art would certainly not expect that all could be used. In fact, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that in the art of treatment of neuronal cells with hedgehog proteins, the specificity of the hedgehog polypeptide is critical in some unknown way, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Additionally, Claim 2 requires the use of a "bioactive fragment" of a hedgehog protein, yet the specification has simply presented an invitation to the skilled artisan to try to find such fragments other than that corresponding to the naturally occurring N-terminal autoproteolytic fragment (e.g. claim 4). The art recognizes that it is this fragment that is required for activity and

that even small deletions of it abolish activity, see Marti, S. et al., Nature 375(322-325)1995, particularly col 1 of page 323 and Figure 1a. Further, the claims encompass variants of the disclosed sonic hedgehog polypeptides, i.e., the specification contemplates such variants as being encompassed by the term "hedgehog polypeptide" (see pages 31-36 for example), yet the specification has not provided sufficient guidance as to how to make such variants. One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a hedgehog polypeptide, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to improve the survival of cholinergic neurons. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g.

such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 11 and 12 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5884079 to Ingham et al., in view of Molses et al., Journal of Neuroscience 15(12)8131-8142)1995.

The specification discloses that administration of hedgehog proteins along with certain neurotrophic factors can promote the survival of a variety of neuron cell types, each of which are known in the art to be lost in particular neurodegenerative diseases, e.g. Parkinson, Huntington, and Alzheimer's diseases. A specific embodiment of the instant claims is a method of promoting the survival of cholinergic neurons of the basal forebrain, either *in vivo* or *in vitro*, comprising the co administration of the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. residues 24-197 of SEQ ID NO: 15) and nerve growth factor (NGF) e.g. pages71-75. The specification indicates that such neurons are known to degenerate in Alzheimer's disease, e.g. pages 62-63, and that these neurons are also useful for *in vitro* studies regarding the effects of neurotrophic factors on them (particularly the effect of sonic hedgehog), as is well established in the art. e.g. see page 71.

U.S. Patent No: 5884079 also discloses that the above disorders and associated neurons can be treated with the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. col 46) and that such treatment can be in combination with the administration of an appropriate neurotrophic factor, e.g. CNTF, BDNF or NGF, see col 47, Lines 27- 38. More particularly U.S. Patent No: 5884079 discloses that cholinergic neurons of the basal forebrain (those of the nucleous basalis), that degenerate in Alzheimer's disease, can be treated with sonic hedgehog proteins (col 46, L38-47). U.S. Patent No: 5884079 does not, however, specifically state which additional

neurotrophic factors would be appropriate to use in the context of Alzheimer's disease. Specifically, U.S. Patent No: 5884079 does not disclose that NGF is trophic for the cholinergic neurons of the basal forebrain as is required by the embodiment of the instant claims referred to above. However, an artisan of ordinary skill appreciates that the survival-promoting effects of NGF on cholinergic neurons of the basal forebrain is well established and old in the art, see Molses et al. who teach that treatment of rats *in vivo* with NGF promotes the survival of basal forebrain cholinergic neurons (see the Abstract).

Therefore, it would be obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, to promote the survival of cholinergic neurons of the basal forebrain (nucleous basalis) by administering a trophic amount of the autoproteolytic fragment of sonic hedgehog and another appropriate neurotrophic factor including CNTF, BDNF and NGF, as taught and suggested by Patent No: 5884079 (cols 46-47) and to use NGF as the particular neurotrophic factor as taught by Molses et al. The motivation to do so is provided by Patent No: 5884079 wherein it is taught that neuronal degenerative disorders such as Alzheimer's disease can be treated with sonic hedgehog in combination with appropriate neurotrophic factors (cols 46-47) and Molses et al. who teach that NGF is an appropriate factor to use on the particular neurons involved in Alzheimer's disease, e.g. the cholinergic neurons of the basal forebrain, see the Abstract.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Winkler, J. et al., Journal of Molecular Medicine 76(555-567)1998 establish the physical feasibility (if not the safety) of treating human Alzheimer's patients with intraventricularly administered NGF, which would not otherwise cross the blood-brain barrier, see page 559 bridging 560.

No claims are allowable.

Please note the new official fax number below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

October 24, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600